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PATENT TRADEMARK OFFICE

PATENT
Attorney Docket No. 08888.0556

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Pierre WILS *et al.*

Application No.: 09/153,838

Filed: September 15, 1998

For: PURIFICATION OF PLASMID DNA OF PHARMACEUTICAL QUALITY

Group Art Unit: 1636

Examiner: J. Ketter

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REQUEST FOR RECONSIDERATION UNDER 37.C.F.R. § 1.111

In reply to the Office action mailed March 13, 2003, Applicants submit the following remarks in this request for reconsideration. This reply is due by June 13, 2003, and is timely filed.

The Office indicates that claims 2-11 and 13-22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base and any intervening claims. Office action, page 3. The previously-indicated allowability of claims 1 and 12 has been withdrawn in view of a newly discovered reference. *Id.*, page 2.

Based on this reference by Johnson *et al.*, Large-Scale Isolation of Plasmid DNA and Purification of λ Phage DNA Using Hydroxylapatite Chromatography, Analytical Biochemistry, 132:20-25 (1983) ("Johnson"), the Office has rejected claims 1 and 11 as

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allegedly anticipated under 35 U.S.C. § 102(b). *Id.* According to the Office, Johnson teaches purification of plasmid DNA from a lysate of *Escherichia coli* by binding it to a hydroxylapatite column, washing the column, and eluting the plasmid. The claims, as interpreted by the Office, "are drawn to a method of purifying double-stranded DNA comprising lysing cells followed by separation of the DNA from other materials on a hydroxyapatite column." *Id.* Respectfully, the Office is reading a term out of the claims. When this term is considered, it is clear that Johnson does not teach (or suggest) each and every limitation of claims 1 and 12.

The claims are directed to "a process for purifying double-stranded DNA . . . using ceramic hydroxyapatite column chromatography." According to the specification, the ceramic form of hydroxyapatite is superior for this use:

> The invention relates, first of all, to a process for purifying double stranded DNA, which process enables large quantities of plasmid DNA of pharmaceutical purity to be obtained very rapidly and involves a chromatographic step on a column of hydroxyapatite which is in ceramic form. While hydroxyapatite in crystalline form was already disclosed, the use of this hydroxyapatite was difficult and limited owing to its fragility. The ceramic form is much more resistant both physically and chemically.

Specification, page 3, lines 10-16.

Johnson does not teach (or suggest) using the ceramic form of hydroxyapatite. Johnson teaches using crystalline hydroxyapatite.

Johnson prepared his chromatography column using "Fast Flow" hydroxylapatite obtained from Calbiochem. Johnson, page 21, sentence bridging first and second columns. "Fast Flow" is not a ceramic hydroxyapatite. It is crystalline. This is evident from Exh. 1, which is a protocol obtained from Calbiochem's web site describing chromatography using the "Fast Flow" product. The nature of this hydroxyapatite is

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described in the section on "Re-hydration," which advises the user to "[g]ently swirl to thoroughly re-suspend the **crystals**." Emphasis added. Crystalline hydroxyapatite, as the specification explains, is not ceramic hydroxyapatite as recited in the claims.

Therefore, Johnson does not teach (or suggest) the invention of claims 1 and 12. Applicants request that the Office reconsider and withdraw this rejection.

In view of the above remarks, Applicants submit that this application is in condition for allowance. An early and favorable action is earnestly solicited.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: May 15, 2003

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CALBIOCHEM®

Hydroxylapatite, Fast Flow

Cat. No. 391947

Protocol

Re-hydration:
Determine the amount of hydroxylapatite necessary for the intended application. Re-hydrate with 4-6 volumes of starting buffer, such as low ionic strength phosphate buffer, pH >5.5. Gently swirl to thoroughly re-suspend the crystals. Allow the slurry to settle. Decant the excess buffer to approximately give an equal volume of buffer to settled hydroxylapatite. Gently re-suspend for a second time in an equal volume of buffer before use.

Packing the Column:
Close the outlet and half-fill the column with starting buffer. Pour the desired amount of fully suspended hydroxylapatite through an attached filling funnel and allow the suspension to settle. After the hydroxylapatite has stabilized, open the column and pour at lease two bed volumes of starting buffer through the column at the appropriate hydrostatic pressure. Prior to the addition of sample, conductivity, pH, or absorbance of the effluent can be used to confirm column equilibration.

Sample Application and Elution:
In general, samples are loaded on the hydroxylapatite in low ionic strength phosphate buffers and are eluted with stepwise or gradient concentration increases. The integrity of the column packing and an accurate measure of the void volume can be determined by applying a small amount of low molecular weight sample which does not bind to hydroxylapatite (e.g. 0.01% methyl orange). This will provide a visual check of uniformity as it passes through the column.

Regeneration of Hydroxylapatite:
High ionic strength phosphate buffer (400-500 mM) is normally sufficient to desorb most material from hydroxylapatite. The use of a high salt solution (1-2 M NaCl), followed by extensive re-equilibration, may help in the removal of contaminants. If necessary, the contaminated top portion of a hydroxylapatite column may be removed, and the column re-packed before subsequent use.

References: Nguyen, L.B., et al. 1990. *J. Biol. Chem.* **265,** 4541.
Schott, K., et al. 1990. *J. Biol. Chem.* **265,** 4204.
Hirano, H., et al. 1985. *Anal. Biochem.* **150,** 228.
Gorbunoff, M.J. 1984. *Anal. Biochem.* **136,** 433.

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